Agency for Healthcare Research and Quality
Advancing Excellence in Health Care

NATIONAL GUIDELINE CLEARINGHOUSE

General

Guideline Title

Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for dihydropyrimidine dehydrogenase genotype and fluoropyrimidine dosing: 2017 update.

Bibliographic Source(s)

Amstutz U, Henricks LM, Offer SM, Barbarino J, Schellens JHM, Swen JJ, Klein TE, McLeod HL, Caudle KE, Diasio RB, Schwab M. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for dihydropyrimidine dehydrogenase genotype and fluoropyrimidine dosing: 2017 update. Clin Pharmacol Ther. 2018 Feb;103(2):210-6. [41 references] PubMed

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Caudle KE, Thorn CF, Klein TE, Swen JJ, McLeod HL, Diasio RB, Schwab M. Clinical Pharmacogenetics Implementation Consortium guidelines for dihydropyrimidine dehydrogenase genotype and fluoropyrimidine dosing. Clin Pharmacol Ther. 2013 Dec;94(6):640-5. [40 references]

This guideline meets NGC's 2013 (revised) inclusion criteria.

NEATS Assessment

National Guideline Clearinghouse (NGC) has assessed this guideline's adherence to standards of trustworthiness, derived from the Institute of Medicine's report Clinical Practice Guidelines We Can Trust.

= Poor = Fair = Good = Very Good = Excellent

Assessment	Standard of Trustworthiness
YES	Disclosure of Guideline Funding Source
	Disclosure and Management of Financial Conflict of Interests

	Guideline Development Group Composition
YES	Multidisciplinary Group
UNKNOWN	Methodologist Involvement
▮▯▯▯▯	Patient and Public Perspectives
	Use of a Systematic Review of Evidence
▮▮▮▮▯	Search Strategy
▮▮▮▮▯	Study Selection
▮▮▮▯▯	Synthesis of Evidence
	Evidence Foundations for and Rating Strength of Recommendations
▮▮▮▮▯	Grading the Quality or Strength of Evidence
▮▮▮▮▮	Benefits and Harms of Recommendations
▮▮▮▮▯	Evidence Summary Supporting Recommendations
▮▮▮▮▮	Rating the Strength of Recommendations
▮▮▮▮▮	Specific and Unambiguous Articulation of Recommendations
▮▮▯▯▯	External Review
▮▮▮▮▯	Updating

Recommendations

Major Recommendations

The strength of therapeutic recommendations (Strong, Moderate, Optional) is defined at the end of the "Major Recommendations" field.

Gene: *DPYD*

Genetic Test Interpretation

Evidence supporting dihydropyrimidine dehydrogenase (DPD) function associated with known *DPYD* variants is summarized in the *DPYD* Allele Functionality Table available on the Clinical Pharmacogenetics Implementation Consortium (CPIC) Web site (see the "Availability of Companion Documents" field). The relationship between *DPYD* genotype and phenotype has only been clearly established for a few variants, whereas the functional impact of many rare variants has been only assessed *in vitro*. Thus, the *DPYD* Allele Functionality Table was divided into sections according to the strength of evidence supporting the assigned allele function: Strong evidence supporting function (from both *in vitro* and clinical studies); moderate evidence supporting function (from *in vitro* and clinical/*ex vivo* studies); *in vitro* data only and/or limited clinical/*ex vivo* data supporting function; uncertain function (conflicting or insufficient evidence supporting function, currently not considered actionable). For each variant, an activity score

similar to that described in reference 12 in the original guideline document was applied: 1 for normal function, 0.5 for decreased function, and 0 for no function variants (including variants with minimal DPD activity).

Table 1 below summarizes the likely DPD phenotype based on genotype. The DPD phenotype is assigned using a gene activity score (*DPYD*-AS), calculated as the sum of the activity scores of the two *DPYD* variants with the lowest variant activity score (based on the *DPYD* Allele Functionality Table available on the CPIC Web site). Briefly, carriers of two no function variants are classified as *DPYD* poor metabolizers (*DPYD*-AS: 0); carriers of one no function or decreased function variant are considered *DPYD* intermediate metabolizers (*DPYD*-AS: 1 or 1.5), and those with only normal function variants are classified as *DPYD* normal metabolizers (*DPYD*-AS: 2). If two different decreased/no function variants are present, they are presumed to be on different gene copies. Irrespective of the presence of decreased/no function variants, patients may carry multiple normal function variants. Common normal function variants may be located on the same gene copy as other normal function variants or decreased/no function variants (see Supplement for further details [see the "Availability of Companion Documents" field]). For example genotype to phenotype interpretations see the Genotype-Phenotype Table, available on the CPIC Web site (see the "Availability of Companion Documents" field).

To ensure correct test interpretation for the transversion variants c.1129–5923C>G and c.2846A>T, the strand to which alleles are assigned needs to be considered. In this guideline, allele designations are relative to the coding deoxyribonucleic acid (DNA) reference sequence (NM_000110.3) and thus the decreased function (i.e., minor) alleles are c.1129–5923G and c.2846T, respectively.

Table 1. Assignment of Likely DPD Phenotypes Based on *DPYD* Genotype

Likely Phenotype	Activity Score[a]	Genotypes[b]	Examples of Genotypes[c]
DYPD normal metabolizer	2	An individual carrying two normal function alleles.	c.[=];[=], c.[85T>C];[=], c.[1627A>G];[=]
DYPD intermediate metabolizer	1 or 1.5	An individual carrying one normal function allele plus one no function allele or one decreased function allele, or an individual carrying two decreased function alleles.	c.[1905+1G>A];[=], c.[1679T>G];[=], c.[2846A>T];[=]; c.[1129–5923C>G];[=][d]; c.[1129–5923C>G];[1129–5923C>G][d]; c.[2846A>T];[2846A>T]
DYPD poor metabolizer	0 or 0.5	An individual carrying two no function alleles or an individual carrying one no function plus one decreased function allele.	c.[1905+1G>A];[1905+1G>A], c.[1679T>G];[1679T>G], c.[1905+1G>A];[2846A>T] c.[1905+1G>A]; [1129-5923C>G]

[a]Calculated as the sum of the two lowest individual variant activity scores. See text in the original guideline document for further information. [b]Allele definitions, assignment of allele function and references can be found on the CPIC Web site (*DPYD* Allele Functionality Table; see the "Availability of Companion Documents" field); [c]HGVS nomenclature using the reference sequence NM_000110.3. [d]Likely HapB3 causal variant. See *DPYD* Allele Functionality Table for other HapB3 proxy SNPs.

Available Genetic Test Options

Testing options for *DPYD* genotype range from targeted analysis of selected variants to resequencing of the complete coding regions. In the context of 5-fluorouracil toxicity, at present most tests focus on the four most common and well-established risk variants (c.1905+1G>A, c.1679T>G, c.2846A>T, c.1129–5923C>G) or a subset thereof. Additional information about commercially available genetic testing options can be found at the Genetic Testing Registry Web site .

Incidental Findings

Individuals who harbor one copy of a no function *DPYD* variant can be considered to have carrier status for an inborn error of metabolism and consideration should be given to its potential effects on offspring. Patients homozygous for inactivating variants of *DPYD* have complete dihydropyrimidine dehydrogenase

deficiency, a clinically heterogeneous autosomal recessive disorder of pyrimidine metabolism that shows wide variability of clinical presentations, ranging from no symptoms to severe convulsive disorders with motor and mental retardation.

Other Considerations

Some of the testing options for 5-fluorouracil toxicity also include testing for other gene variants in *TYMS* and *MTHFR*. To date, however, the clinical utility of these genotypes is unclear (see further details in Supplement), and predictive dosing strategies have yet to be successfully applied. For a summary of pharmacogenomic studies of 5-fluorouracil, see the PGx Research tab at https://www.pharmgkb.org/chemical/PA128406956/literature .

There are alternative or complementary tests to *DPYD* genotyping that assess DPD activity directly in peripheral mononuclear cells or indirectly through the endogenous dihydrouracil/uracil ratio (UH2/U) in plasma, or using a uracil loading test. See Ref. 16 in the original guideline document for a review of these methods. The application of a combined genotype/phenotype approach including selected *DPYD* risk variants has been shown to reduce toxicity in a prospective study. However, such tests are not widely available. Furthermore, the mean and range of the pretherapeutic endogenous UH2/U ratio varied widely between studies, limiting its practical use, and several studies did not observe a strong correlation between the UH2/U ratio and 5-fluorouracil plasma concentrations.

Drugs: Fluoropyrimidines

Prescribing Recommendations

Table 2 below summarizes the genetics-based dosing recommendations fluoropyrimidines using the calculated *DPYD* activity score (*DPYD*-AS). The strength of the prescribing recommendations is based on the known impact of some variants (c.1905+1G>A, c.1679T>G, c.2846A>T, c.1129–5923C>G) on DPD activity, the demonstrated relationship between DPD activity and 5-fluorouracil clearance, and between 5-fluorouracil exposure and its toxic effects. Patients who are heterozygous for *DPYD* decreased/no function variants demonstrate partial DPD deficiency and should receive reduced starting doses. Prospective genotyping of c.1905+1G>A followed by a 50% dose reduction in heterozygous carriers resulted in a rate of severe toxicity comparable to noncarriers. This study thus demonstrated that *DPYD* genetic testing can reduce the occurrence of severe fluoropyrimidine-related toxicity, and that a dose reduction of 50% is suitable for heterozygous carriers of no function variants (*DPYD*-AS: 1). For decreased function variants, evidence is limited regarding the optimal degree of dose reduction. For c.2846A>T, a small retrospective study observed that the average capecitabine dose in heterozygous carriers was reduced by 25% compared to noncarriers. In a small prospective study, five patients carrying c.1236G>A (proxy for c.1129–5923C>G) were safely treated with a 25% reduced capecitabine starting dose. This suggests that heterozygous carriers of decreased function variants (*DPYD*-AS: 1.5) may tolerate higher doses compared to carriers of no function variants (*DPYD*-AS: 1). In patients with *DPYD*-AS of 1.5, the individual circumstances of a given patient should therefore be considered to determine if a more cautious approach (50% starting dose followed by dose titration), or an approach maximizing potential effectiveness with a potentially higher toxicity risk (25% dose reduction) is preferable. Of note, both studies indicating the suitability of a 25% dose reduction in decreased function variant carriers included only patients receiving capecitabine and no data are currently available for infusional 5-fluorouracil.

Given that some patients carrying decreased or no function variants tolerate normal doses of 5-fluorouracil, to maintain effectiveness, doses should be increased in subsequent cycles in patients experiencing no or clinically tolerable toxicity in the first two chemotherapy cycles or with subtherapeutic plasma concentrations. Similarly, doses should be decreased in patients who do not tolerate the starting dose.

In *DPYD* poor metabolizers (*DPYD*-AS: 0.5 or 0), it is strongly recommended to avoid use of 5-fluorouracil-containing regimens. However, if no fluoropyrimidine-free regimens are considered a suitable therapeutic option, 5-fluorouracil administration at a strongly reduced dose combined with early therapeutic drug monitoring may be considered for patients with *DPYD*-AS of 0.5. It should be noted, however, that no

reports of the successful administration of low-dose 5-fluorouracil in *DPYD* poor metabolizers are available to date. Assuming additive effects of decreased and no function alleles (*DPYD*-AS: 0.5), it is estimated that a dose reduction of at least 75% would be required (i.e., starting dose <25% of normal dose). Furthermore, in such cases a phenotyping test (see "Other Considerations," above) is advisable to estimate DPD activity and a starting dose.

The U.S. Food and Drug Administration (FDA) and the Health Canada Santé Canada (HCSC) have added statements to the drug labels for 5-fluorouracil and capecitabine that warn against use in patients with DPD deficiency, and prescribing recommendations for 5-fluorouracil, capecitabine, and tegafur are also available from the Dutch Pharmacogenetics Working Group.

Tegafur

Tegafur (not available in the United States), is a prodrug of 5-fluorouracil administered in combination with uracil (UFT) or with gimeracil and oteracil (S-1, Teysuno). For these therapies, evidence regarding the impact of *DPYD* variants on toxicity risk is very limited. Given the inhibition of DPD by the coadministered uracil or gimeracil, dose requirements of patients carrying decreased/no function *DPYD* variants are currently unknown. The dosing recommendations provided here currently apply only to 5-fluorouracil and capecitabine. As such, tegafur is rated as a CPIC "no recommendation" (see Supplement for definition).

Pediatrics

At the time of this writing, data on the possible role of *DPYD* genetic variation in 5-fluorouracil toxicity in pediatric patient populations are extremely scarce; however, there is no evidence to suggest that 5-fluorouracil pharmacokinetics differ from adult patients, and thus no evidence that *DPYD* variants would affect 5-fluorouracil metabolism differently in children.

Table 2. Recommended Dosing of Fluoropyrimidines[a] by DPD Phenotype

Phenotype	Implications for Phenotypic Measures	Dosing Recommendations	Classification of Recommendations[b]
DPYD normal metabolizer	Normal DPD activity and "normal" risk for fluoropyrimidine toxicity.	Based on genotype, there is no indication to change dose or therapy. Use label-recommended dosage and administration.	Strong
DPYD intermediate metabolizer	Decreased DPD activity (leukocyte DPD activity at 30% to 70% that of the normal population) and increased risk for severe or even fatal drug toxicity when treated with fluoropyrimidine drugs.	Reduce starting dose based on activity score followed by titration of dose based on toxicity[c] or therapeutic drug monitoring (if available). Activity score 1: Reduce dose by 50% Activity score 1.5: Reduce dose by 25% to 50%	Activity score 1: Strong Activity score 1.5: Moderate
DPYD poor metabolizer	Complete DPD deficiency and increased risk for severe or even fatal drug toxicity when treated with fluoropyrimidine drugs.	Activity score 0.5: Avoid use of 5-fluorouracil or 5-fluorouracil prodrug-based regimens. In the event, based on clinical advice, alternative agents are not considered a suitable therapeutic option, 5-fluorouracil should be administered at a strongly reduced dose[d] with early therapeutic drug monitoring.[e] Activity score 0: Avoid use of 5-fluorouracil or 5-fluorouracil prodrug-based regimens.	Strong

[a]5-fluorouracil or capecitabine. [b]See the "Rating Scheme for the Strength of the Recommendations" field. [c]Increase the dose in patients experiencing no or clinically tolerable toxicity in the first two cycles to maintain efficacy; decrease the dose in patients who do not tolerate the starting dose to minimize toxicities. [d]If available, a phenotyping test (see main text for further details) should be considered to

estimate the starting dose. In the absence of phenotyping data, a dose of <25% of the normal starting dose is estimated assuming additive effects of alleles on 5-FU clearance. [e]Therapeutic drug monitoring should be done at the earliest timepoint possible (e.g., minimum timepoint in steady state) in order to immediately discontinue therapy if the drug level is too high.

Recommendations for Incidental Findings

Symptoms of DPD deficiency generally present in childhood and, in the majority of patients, within the first year of life. Currently, a correlation between symptom severity and DPD function and/or genetics has not been established. However, early phenotypic (e.g., urine screening of uracil and its degradation products) and/or genetic testing (pre- or postnatal) of offspring of *DPYD* no function variant carriers could aid in early diagnosis to avoid a lengthy diagnostic odyssey.

Other Considerations

Recently, a common polymorphism (rs895819A>G) in the *DPYD*-regulatory microRNA miR-27a was associated with lower DPD activity and with fluoropyrimidine-related toxicity in patients carrying decreased function *DPYD* variants. This suggests that this *MIR27A* variant may allow further stratification of *DPYD* risk variant carriers. However, pharmacokinetic studies combining *DPYD* and *MIR27A* genotype are needed before dosing recommendations that incorporate *MIR27A* genotype can be made.

Other genetic variation and patient characteristics such as sex and age have also been associated with 5-fluorouracil toxicity; however, the clinical utility of these associations are not fully understood (see Supplement for more information). Disease and treatment regimens may influence the overall risk of toxicity, and thus also the absolute risk of toxicity in carriers of *DPYD* decreased/no function variants. However, the association of *DPYD* variants with 5-fluorouracil-related toxicity has been found to be fairly consistent across treatment regimens.

Pharmacokinetically guided dosing of 5-fluorouracil has been shown to result in an increase in the proportion of patients with 5-fluorouracil exposure (area under the curve [AUC]) within the targeted therapeutic range and a reduced number of 5-fluorouracil-related adverse effects. In particular, to avoid underdosing of patients with genotype-based dose reductions who tolerate higher 5-fluorouracil doses, follow-up therapeutic drug monitoring is recommended.

Definitions

Strength of Therapeutic Recommendations

Strong: The evidence is high quality and the desirable effects clearly outweigh the undesirable effects.

Moderate: There is a close or uncertain balance as to whether the evidence is high quality and the desirable clearly outweigh the undesirable effects.

Optional: The desirable effects are closely balanced with undesirable effects and there is room for differences in opinion as to the need for the recommended course of action.

No recommendation: There is insufficient evidence, confidence, or agreement to provide a recommendation to guide clinical practice at this time.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Cancer

Guideline Category

Prevention

Risk Assessment

Treatment

Clinical Specialty

Medical Genetics

Oncology

Pharmacology

Intended Users

Advanced Practice Nurses

Nurses

Pharmacists

Physician Assistants

Physicians

Guideline Objective(s)

To provide information for the interpretation of clinical dihydropyrimidine dehydrogenase (*DPYD*) genotype tests so that the results can be used to guide dosing of fluoropyrimidines (5-fluorouracil and capecitabine)

Note: Detailed guidelines for the use of fluoropyrimidines and their clinical pharmacology are beyond the scope of this document.

Target Population

Patients requiring fluoropyrimidine chemotherapy

Interventions and Practices Considered

Dosing of fluoropyrimidines (5-fluorouracil, capecitabine) based on dihydropyrimidine dehydrogenase (*DPYD*) genotype

Major Outcomes Considered

Rate and severity of fluoropyrimidine-related adverse events including toxicity

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Retrieval of the Evidence Linking Genotype to Drug Variability

The PharmGKB Scientific Curator, the Clinical Pharmacogenetics Implementation Consortium (CPIC) coordinator or authors with experience in literature or systematic review conduct the literature review and present the results to the writing committee. A search of PubMed and OVID MEDLINE is performed using the keywords for the gene and drug of interest, for example: (gene name) OR (gene symbol) OR (dbSNP rs number) OR (gene common names) AND (drug name OR drug class name). Furthermore, papers listed on PharmGKB are cross-checked as there may be annotations for the papers and/or additional publications. Where available, evidence evaluating the outcomes when prescribing has been altered based on genetic testing is included. For most gene-drug pairs, randomized controlled trials comparing clinical outcomes with genotype-guided dosing versus conventional dosing are not available.

Literature Review

2013 Guideline

A literature search of the PubMed® database (1966 to March 2013) using the keywords ((DPD OR DPYD OR Dihydropyrimidine Dehydrogenase) AND (fluorouracil OR 5-FU OR fluoropyrimidines OR capecitabine OR tegafur) AND genotype) was performed and results were limited to those available in English. Further articles were found via the reference sections of reviews. Using these search terms, 104 publications were identified. Study inclusion criteria included publications that included analyses for the association between *DPYD* genotypes (c.1905+1G>A , c.1679T>G, and c.2846A>T) and metabolism of dihydropyrimidines and adverse drug events or clinical outcomes. Non-English manuscripts were excluded.

2017 Guideline

The authors searched the PubMed® database as described above between 1966 and March 2017. The 2013 literature review was repeated to include all known *DPYD* genotypes. Using these search terms, 150 publications were identified.

Number of Source Documents

2013 Guideline

Following application of the inclusion criteria, 30 publications were reviewed and included in the evidence tables.

2017 Update

Following application of the inclusion criteria, 49 publications were reviewed and included in the evidence tables. An additional 42 studies were identified from the reference sections of reviews and other published papers, and included in the evidence tables, bringing the total included studies to 91 (see Supplemental Table S1 [see the "Availability of Companion Documents" field]).

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Level of Evidence

High: Evidence includes consistent results from well-designed, well-conducted studies.

Moderate: Evidence is sufficient to determine effects, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies; generalizability to routine practice; or indirect nature of the evidence.

Weak: Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information.

Methods Used to Analyze the Evidence

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

The Clinical Pharmacogenetics Implementation Consortium's (CPIC's) dosing recommendations (see Table 2 in the original guideline document) are based on weighting the evidence from a combination of preclinical functional and clinical data, as well as on some existing disease-specific consensus guidelines. Some of the factors that are taken into account include *in vivo* clinical outcome for reference drug, *in vivo* pharmacokinetic and pharmacodynamic (PK/PD) studies for reference drug, and *in vitro* enzyme activity with probe substrate only.

The evidence summarized in Supplemental Table S5 (see the "Availability of Companion Documents" field) is graded using a scale slightly modified from Valdes et al. (see the "Rating Scheme for the Strength of the Evidence" field).

Summarization and Presentation of the Evidence Linking Genotype to Drug Variability

Publications supporting a major finding are usually considered as a group and scored by members of the writing committee based on the totality of the evidence supporting that major finding. Thus, it is possible for an evidentiary conclusion based on many papers, each of which may be relatively weak, to be graded as "moderate" or even "strong," if there are multiple small case reports or studies that are all supportive with no contradictory studies. The rating scheme (see the "Rating Scheme for the Strength of the Evidence" field) uses a scale modified slightly from Valdes et al. Primary publications are summarized in the Evidence Table which is published in the manuscript supplemental material (see the "Availability of Companion Documents" field). It is the writing committee's evaluation of this evidence that provides the basis for the therapeutic recommendation(s).

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Identification of Content Experts and Formation of Writing Committee

Once a guideline topic has been approved by Clinical Pharmacogenetics Implementation Consortium (CPIC) members and the Steering Committee, a senior author is identified through self-nomination or by request of the CPIC Steering Committee. The senior author takes responsibility for forming the writing committee and completing the guideline. The writing committee is multidisciplinary, comprising a variety

of scientists, pharmacologists, and clinicians (e.g., pharmacists and physicians). Authors will have a track record of publication and/or expertise in the specific topic area of the guideline. PharmGKB assigns at least one Scientific Curator to each CPIC guideline writing committee who has expertise in searching, compiling and evaluating the evidence for gene-drug associations, and making it computable and available on the PharmGKB Web site. Furthermore, PharmGKB curators often take primary responsibility for completing background gene and drug summaries, assigning likely phenotypes based on genotypes (i.e., "Table 1" in guidelines), literature review, as well as preparing supplementary material provided in each guideline (i.e., genotypes that constitute the star [*] alleles or haplotypes, frequencies of alleles in major race/ethnic groups, genetic test interpretation and availability, and evidence linking genotype with phenotype).

Development of Therapeutic Recommendation and Assignment of Strength of the Recommendation

The writing committee discusses the evaluation of the literature and develops a draft recommendation via Web conferences and email communication. CPIC's therapeutic recommendations are based on weighing the evidence summarized in the supplementary Evidence Table from a combination of preclinical functional and clinical data, as well as on any existing consensus guidelines. Evidence related to the suitability of alternative medications or dosing that may be used based on genetics must be weighed in assigning the strength of the recommendation. Overall, the therapeutic recommendations are simplified to allow rapid interpretation by clinicians and are presented in the Table 2 of each guideline and occasionally in an algorithm.

To assign strength to a recommendation, CPIC uses a transparent three category system (see the "Rating Scheme for the Strength of the Recommendations" field) for rating recommendations that was adopted with slight modification from the rating scale for evidence-based recommendations on the use of antiretroviral agents (http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf ; see the "Rating Scheme for the Strength of the Evidence" field). Each recommendation also includes an assessment of its usefulness in pediatric patients.

CPIC guidelines currently focus on gene-drug pairs for which at least one of the prescribing recommendations is actionable (e.g., recommendation to alter a dose or consider an alternative drug based on the genotype-phenotype relationship). For these and many other gene-drug pairs, PharmGKB also contains clinical annotations that are genotype-based summaries of the association between a drug and a particular variant. Each clinical annotation is assigned a level of evidence depending on population, replication, effect size and statistical significance.

Refer to "Incorporation of pharmacogenomics into routine clinical practice: the Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline development process" (see the "Availability of Companion Documents" field) for additional information.

Rating Scheme for the Strength of the Recommendations

Strength of Therapeutic Recommendations

Strong: The evidence is high quality and the desirable effects clearly outweigh the undesirable effects.

Moderate: There is a close or uncertain balance as to whether the evidence is high quality and the desirable clearly outweigh the undesirable effects.

Optional: The desirable effects are closely balanced with undesirable effects and there is room for differences in opinion as to the need for the recommended course of action.

No recommendation: There is insufficient evidence, confidence, or agreement to provide a recommendation to guide clinical practice at this time.

Cost Analysis

Analyses of cost-effectiveness are beyond the scope of the guideline.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

Internal and External Review, Comment, and Approval Process

Once the writing committee has completed and approved a draft guideline, the draft guideline is circulated to the Clinical Pharmacogenetics Implementation Consortium (CPIC) co-leaders and coordinator for content review. The guideline is reviewed for compliance with the CPIC Standard Operating Procedures and required format. The guideline draft is then discussed on a CPIC conference call with all CPIC members and circulated to the members for further review and approval. At each stage, feedback is considered for incorporation into the guideline and/or revision of the guideline, as supported by the available evidence and expert clinical judgment of the senior author and writing committee. Finally, the guideline manuscript under goes typical external scientific peer review by the journal prior to publication. Current agreements with the American Society for Clinical Pharmacology and Therapeutics give the journal *Clinical Pharmacology and Therapeutics* the first right of refusal for publication of CPIC guidelines; as part of this agreement, the guidelines are freely posted to PharmGKB immediately upon publication. In general *Clinical Pharmacology and Therapeutics* uses a minimum of two external expert peer-reviewers and an editorial board member with content expertise as reviewers for each CPIC guideline.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The evidence summarized in Supplemental Table S1 (see the "Availability of Companion Documents" field) is graded using a scaled modified slightly from Valdes et al.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

The benefit of dihydropyrimidine dehydrogenase (*DPYD*) genotyping has been demonstrated in a prospective study, which showed a reduced occurrence of severe 5-fluorouracil-related toxicity and no toxicity-related deaths in carriers of c.1905+1G>A after genotype-guided dose reduction.

Potential Harms

Not all carriers of dihydropyrimidine dehydrogenase (*DPYD*) decreased/no function variants develop severe toxicity at standard doses. As a consequence, some carriers of such variants may not receive the full benefit of fluoropyrimidine therapy with the recommended dose reductions. To maintain efficacy, it is important to increase the dose in patients experiencing no or clinically tolerable toxicity or with subtherapeutic 5-fluorouracil plasma concentrations. Patients who proceed with 5-fluorouracil therapy may

still experience acceptable lower-grade toxicity that may even be necessary in order to achieve efficacy. A possible risk is the misreporting or misinterpretation of genetic test results.

Qualifying Statements

Qualifying Statements

Caveats: Appropriate Use and/or Potential Misuse of Genetic Tests

The presence of decreased or no function variants does not always result in toxicity. Overall, ~50% of decreased function dihydropyrimidine dehydrogenase (*DPYD*) variant carriers develop severe 5-fluorouracil-related toxicity with standard doses, with estimates varying depending on the overall frequency of toxicity for a given treatment regimen and the number of treatment cycles evaluated. At the same time, patients without a DPYD decreased/no function variant may still experience severe toxicity due to other genetic, environmental, or other factors.

The sensitivity of *DPYD* genetic testing depends on the number of variants investigated. By combining the *DPYD* variants c.1905>A, c.2846A>T, c.1679T>G, c.1129–5923C>G, 20% to 30% of early-onset 5-fluorouracil toxicities can be explained. However, a test that includes only a subset of those *DPYD* variants (e.g., only c.1905+1G>A) has a reduced sensitivity. Finally, given the existence of many additional rare deleterious *DPYD* variants, a genetic test investigating only selected decreased/no function variants does not fully rule out DPD defects.

Disclaimer

Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines reflect expert consensus based on clinical evidence and peer-reviewed literature available at the time they are written and are intended only to assist clinicians in decision making and to identify questions for further research. New evidence may have emerged since the time a guideline was submitted for publication. Guidelines are limited in scope and are not applicable to interventions or diseases that are not specifically identified. Guidelines do not account for individual variations among patients and cannot be considered inclusive of all proper methods of care or exclusive of other treatments. It remains the responsibility of the health-care provider to determine the best course of treatment for a patient. Adherence to any guideline is voluntary, with the ultimate determination regarding its application to be made solely by the clinician and the patient. CPIC assumes no responsibility for any injury or damage to persons or property arising out of or related to any use of CPIC's guidelines or for any errors or omissions.

Implementation of the Guideline

Description of Implementation Strategy

Implementation of This Guideline

The guideline supplement contains resources that can be used within electronic health records (EHRs) to assist clinicians in applying genetic information to patient care for the purpose of drug therapy optimization (see *Resources to incorporate pharmacogenetics into an electronic health record with clinical decision support* sections of the Supplement [see the "Availability of Companion Documents" field]).

Refer to "Incorporation of pharmacogenomics into routine clinical practice: the Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline development process" (see the "Availability of Companion Documents" field) for information on guideline dissemination and connecting the guidelines to practice.

Implementation Tools

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

Staying Healthy

IOM Domain

Effectiveness

Safety

Identifying Information and Availability

Bibliographic Source(s)

Amstutz U, Henricks LM, Offer SM, Barbarino J, Schellens JHM, Swen JJ, Klein TE, McLeod HL, Caudle KE, Diasio RB, Schwab M. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for dihydropyrimidine dehydrogenase genotype and fluoropyrimidine dosing: 2017 update. Clin Pharmacol Ther. 2018 Feb;103(2):210-6. [41 references] PubMed

Adaptation

Not applicable: The guideline was not adapted from another source.

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Guideline Developer(s)

Clinical Pharmacogenetics Implementation Consortium - Independent Expert Panel

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Guideline Committee

Not stated

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Conflict of Interest

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Management of Conflicts of Interest

All authors must declare any funding interests and activities potentially resulting in conflict of interest by written disclosure to the CPIC Steering Committee and writing committee before the approval of the authorship plan. Included are all possible conflicts including spouses/family members in declarations, National Institutes of Health (NIH) funding that could be interpreted to indicate that authors are "advocates" of the recommendations, as well as any sources of revenue from consulting, patents, stock ownership, etc. All conflicts of interest are reported in the guideline manuscript.

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Caudle KE, Thorn CF, Klein TE, Swen JJ, McLeod HL, Diasio RB, Schwab M. Clinical Pharmacogenetics Implementation Consortium guidelines for dihydropyrimidine dehydrogenase genotype and fluoropyrimidine dosing. Clin Pharmacol Ther. 2013 Dec;94(6):640-5. [40 references]

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Available from the Clinical Pharmacogenetics Implementation Consortium (CPIC) Web site .

Availability of Companion Documents

The following are available:

Supplementary material, including tables and methodological information, is available from the Clinical Pharmacogenetics Implementation Consortium (CPIC) Web site .

A variety of resources, including definition, frequency, functionality, and diplotype-phenotype tables; drug mapping; gene resource mapping; and clinical decision support, are available from the CPIC Web site .

Caudle KE, Klein TE, Hoffman JM, et al. Incorporation of pharmacogenomics into routine clinical practice: the Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline development process. Curr Drug Metab. 2014;15(2):209-17. Available from the National Center for Biotechnology Information (NCBI) Web site .

Patient Resources

None available

NGC Status

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